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Efficacy of Bacillus Calmette-Guérin in Cancer Prevention and Its Putative Mechanisms

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Bacillus Calmette-Guérin (BCG) is an attenuated strain of *Mycobacterium bovis*. Although it was developed as a prophylactic vaccine against tuberculosis (TB), researchers have also evaluated it for preventing cancer development or progression. These studies were inspired by the available data regarding the protective effects of microbial infection against cancers and an inverse relationship between TB and cancer mortality. Initial studies demonstrated the efficacy of BCG in preventing leukemia, melanoma and a few other cancers. However, mixed results were observed in later studies. Importantly, these studies have led to the successful use of BCG in the tertiary prevention of non-muscle invasive bladder cancer, wherein BCG therapy has been found to be more effective than chemotherapy. Moreover, in a recently published 60-year follow-up study, childhood BCG vaccination has been found to significantly prevent lung cancer development. In the present manuscript, we reviewed the studies evaluating the efficacy of BCG in cancer prevention and discussed its putative mechanisms. Also, we sought to explain the mixed results of BCG efficacy in preventing different cancers.

Key Words Bacillus Calmette-Guérin, Vaccines, Neoplasms, Prevention, Mechanisms

INTRODUCTION

Cancer has emerged as a major public health threat. Approximately 19.3 million new cancer cases were reported by the Global Cancer Observatory in 2020 [1]. Despite advancements in treatment approaches, death rates for most cancers remain high, specifically when detected at an advanced stage. Also, most treatment approaches to cancer are associated with toxicities, ranging from mild to severe and dose-limiting.

An old proverb says, “prevention is better than cure”. Vaccines, which have significantly reduced the burden of many debilitating and fatal infectious diseases, epitomize this proverb very aptly [2]. However, the use of prophylactic vaccines has met with limited success in the case of cancer, partly due to the lack of suitable cancer antigens. Although many cancer antigens have been described and characterized, they have inherent limitations such as unstable expression pattern, lack of specificity for cancerous cells/tissue or limited presentation by major histocompatibility complex (MHC) molecules [3].

A key feature of most cancers is the evasion of the immune system, wherein established tumors evolve strategies to survive in the face of a fully functional immunity. These strategies include the recruitment of immunosuppressive cells and secretion of immunosuppressive cytokines in tumor milieu, down-regulation of antigen-presenting molecules and elimination/inactivation of $CD8^+$ T lymphocytes [4]. Importantly, the immunosuppressive milieu in established tumors can be reversed using immunostimulatory agents, potentially leading to a state of protection.

Bacillus Calmette-Guérin (BCG) is an attenuated strain of *Mycobacterium bovis* with potent stimulatory activities [5]. Derived at the beginning of the 20th century, BCG was initially used as a prophylactic agent against tuberculosis (TB) [5]. As a part of a long quest to use bacteria or bacterial products for cancer immunotherapy, BCG was also evaluated for its antitutmor efficacy [6]. Clinical and pre-clinical studies have demonstrated mixed results regarding the efficacy of BCG in primary cancer prevention. However, it has been found to be effective in the tertiary prevention of non-muscle invasive bladder cancer (NMIBC), wherein it is administered intravesically after surgical tumor resection [7]. Notably, a recent 60-year follow-up study has demonstrated the efficacy of childhood BCG vaccination in primary prevention of lung cancer

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[8]. A few studies have also re-examined the data pertaining to the antitumor efficacy of BCG [9]. The present manuscript reviews the findings on the efficacy of BCG in cancer prevention and sheds light on the underlying immune mechanisms.

BCG VACCINE

At the beginning of the 20th century, French researchers Albert Calmette and Camille Guérin attenuated *M. bovis* (by sub-culturing it in glycerine-bile-potato medium for nearly 13 years) to develop a TB vaccine [10]. Attenuated strain was first administered to an infant whose mother had died of TB a few hours after giving birth, in 1921 [10]. The infant did not contract TB and exhibited no adverse sequelae. These observations led to an increased interest in the attenuated *M. bovis* strain, named BCG, as a prophylactic vaccine against TB. By 1928, more than 114,000 infants were vaccinated with BCG with no serious complications [10]. Subsequent statistical analyses by Calmette and Guerin showed a fall in TB mortality among the BCG-vaccinated infants. By the late 1940s, multiple studies had provided evidence for the effectiveness of BCG against TB [10].

The use of BCG was stimulated by the World War II as the war was thought to result in the increased TB incidence. Interestingly, as the data regarding the anti-TB efficacy of BCG from different countries had accumulated, it became clear that the efficacy of BCG against TB varies widely in different populations [11]. Various factors including strain variations, nutritional/genetic differences between populations, poor cold-chain maintenance, and prior exposure to environmental mycobacteria (EMb) were suggested to contribute to the variation in BCG efficacy against TB [12]. Animal studies also indicated that prior exposure to EMb compromises the efficacy of BCG against TB and led to 2 hypotheses, viz. blocking and masking hypotheses that have been floated to explain the variable efficacy of BCG [12]. We have also provided an explanation for the variable efficacy of BCG against adult pulmonary TB by taking into account (i) the role of EMb in promoting anti-*Mycobacterium tuberculosis* immune responses and (ii) etiological effect of aggravated immunity in the pathogenesis of *M. tuberculosis* [5]. Accordingly, BCG is ineffective against adult pulmonary TB in the areas of higher EMb abundance, for individuals in these places tend to develop an aggravated antimycobacterial immunity which can destroy granuloma architecture and reactivate latent *M. tuberculosis* infection into the active disease [5].

EVALUATION OF BCG AGAINST CANCER

The initial impetus for using BCG against cancer might be attributed to the scientific knowledge about the inverse relationship between cancer and infectious diseases, including TB at that time. Earlier studies had also documented an association between spontaneous tumor regression and concomitant bacterial infections [13]. Guided by similar observations, Dr. William Coley, a New York-based surgeon used an extract from heat-killed *Streptococcus pyogenes* and *Serratia marcescens* (known as Coley's toxin) to treat a variety of cancers at the beginning of the 20th century [14]. In 1929, Pearl [15] reported higher incidence of healed or active TB in cancer survivors, compared with those in the individuals dying of it. Conversely, a significantly lower incidence of cancer was observed in patients dying of TB, compared with that in similarly matched controls [15].

Old et al. [16] were probably the first to evaluate antitumor efficacy of BCG in an animal model. In a series of experiments performed in the late 1950s, he demonstrated that BCG-infected mice were more resistant to transplantable tumors [16]. In 1970s, Zbar and Tanaka [17] demonstrated that BCG administration led to tumor inhibition in an animal model when its infection occurred at the site of tumor development, and this effect was mediated putatively by a delayed hypersensitivity type of immune response. This study also demonstrated the regression of intradermal tumors, inhibition of lymph node metastases and eradication of nodal micrometastases with intradermal BCG administration in guinea pigs. Based on these observations, Zbar and Rapp [18] formulated the criteria for successful BCG therapy. Accordingly, the success of BCG therapy relies on: (i) close contact between tumor cells and BCG, (ii) immune competence of the host to react to mycobacterial antigens, (iii) a limited tumor burden and (iv) an adequate numbers of viable BCG bacilli [18].

BCG was first used against any cancer in humans in the mid-1930s by Holmgren [19]. In subsequent studies in the 1960s, antitumor efficacy of BCG was evaluated by Villasor [20] and Mathé et al. [21], who reported promising results with BCG as an adjuvant therapy for the treatment of acute lymphoblastic leukemia. These studies generated an increasing interest in BCG, prompting its evaluation against many cancer types including leukemia, malignant melanoma, lung cancer and prostate cancer. Findings from these studies assessing the anticancer efficacy of BCG are discussed in the following sections.

EFFICACY OF BCG IN PRIMARY CANCER PREVENTION

Primary prevention aims to protect against the disease development. Various approaches to primary cancer prevention include minimizing the exposure to hazards/risk-factors, altering life-style, and increasing resistance to disease by immunization. BCG has been evaluated for primary prevention of many cancer types. The first study evaluating BCG against cancer was published in 1936 [19]. However, first claim regarding the efficacy of BCG in primary cancer prevention was made by Davignon et al. [22] in 1970. The authors reported that the leukemia mortality rate in BCG-vaccinated children aged ≤15 years was nearly half of that in unvaccinated chil-

dren in Quebec. However, the epidemiological basis of this study met with criticism, to which authors provided explanations and refined their analyses [23]. Offering some support to the claims of Davignon et al. [23], Waaler [24] noted that the age groups of children with the lowest leukaemia death rates in 3 Scandinavian countries corresponded with the ages at BCG immunization. At the same time, Hems and Stuart [25] observed that the leukaemia mortality rate, which was increasing during the first half of the 20th century, started to decrease as widespread BCG vaccination was introduced in England. Similar results were obtained in the British BCG vaccination trial, wherein the leukaemia mortality rate was 2.4/100,000 amongst vaccinated children compared with 4.1/100,000 amongst tuberculin-negative unvaccinated children [26]. In 1972, Rosenthal et al. [27] found that only one among 54,414 neonatally vaccinated children died of leukaemia before the age of 6 years, compared with 21 among 172,986 unvaccinated children in Chicago. In a subsequent study, the same authors reported a 74% reduction in the incidence of all types of childhood cancers in the same vaccinated population during the first 20 years of life [28].

On the other hand, findings from other investigations were suggestive of no or minimal effect of BCG on cancer prevention. In 1971, Comstock et al. [29] found no differences in the leukaemia mortality rates in a BCG trial in Georgia and Alabama. However, in a later trial in Puerto Rico involving 1 to 18-year-old vaccinated children, a lower incidence of leukaemia, but a higher incidence of Hodgkin's disease and lymphosarcoma were observed in the vaccinated group by the same authors [30]. In 1975, Salonen and Saxén [31] reported comparable rates of childhood leukaemia in BCG-vaccinated and unvaccinated children in Finland. In a follow-up study on BCG-vaccinated children, Skegg showed no association between BCG vaccination and the incidence of leukaemia, Hodgkin's disease and other malignancies in New Zealand [32].

However, further studies suggested that the effects of BCG vaccination on cancer prevention could not be so easily dismissed. In a study in Finland, it was demonstrated that both BCG vaccination and natural *M. tuberculosis* infection conferred some protection against leukaemia [33]. Similarly, detailed studies in Austria conducted by Ambrosch et al. [34,35] showed that BCG vaccination decreased leukemia mortality and case fatality, delayed the disease manifestation, prolonged the survival/improved the 5-year survival rates and reduced the incidence of myeloblastic leukaemia in children up to 5 years of the age. Similar protective effects of BCG against leukemia were also reported in Israel [36]. In 2016, a meta-analysis involving 12 studies also deduced some evidence for the protective effects of BCG against childhood leukemia [9].

BCG had also been evaluated for its protective efficacy against other cancers. In the epidemiological studies conducted in several European countries and Israel, it was observed that vaccinations with BCG and/or vaccinia (and also the occurrence of some uncommon but severe infections) were associated with a significantly reduced risk of developing melanoma in future [37-40]. Moreover, prior immunization with BCG and/or vaccinia was found to reduce the risk of death during the study period of at least 5 years in melanoma patients [40]. Based on these studies, not being vaccinated with either BCG or vaccinia had been considered as a risk factor for melanoma [37]. Only a few studies examined the efficacy of BCG in protection against melanoma in subsequent years. Notably, a recent register-based case-cohort study following individuals from 18 to 49 years, demonstrated no strong beneficial effects of smallpox and BCG vaccination against cutaneous malignant melanoma among adult Danes. However, the study estimates did not contradict a potential modest beneficial effect of neonatal vaccination against this condition [41].

Interestingly, a study has demonstrated significant effectiveness of BCG in preventing lung cancer development [8]. In this study, 2,963 children (1,540 in the BCG vaccine group [median age at vaccination, 8 years] and 1,423 in the placebo group) were followed for 60 years. It was observed that the rate of lung cancer was significantly lower in the BCG group, compared with the placebo group [8]. However, the overall rates of cancer development, including that of lymphoma and leukemia were not significantly different in the BCG versus placebo recipients.

EFFICACY OF BCG IN TERTIARY CANCER PREVENTION

Tertiary cancer prevention aims at preventing relapse or prolonging relapse-free survival of cancer patients. BCG has been evaluated for tertiary prevention of many cancer types including melanoma, prostate cancer, lung cancer and bladder cancer. These studies have demonstrated variable success rates of BCG in tertiary cancer prevention. Findings on the BCG efficacy in tertiary prevention of specific cancers are presented below.

Bladder cancer

Bladder cancer begins in the cells of the bladder- a hollow, muscular, urine-storing organ in the lower abdomen. Among various cancer types, NMIBC (also called superficial bladder cancer) has shown the most significant response to BCG. Ground for evaluating BCG against bladder cancer was prepared in 1966 with the observations of immune reactions in guinea pig urinary bladders by Coe and Feldman [42]. In 1975, deKernion et al. [43] reported successful BCG therapy of an isolated metastasis of malignant melanoma to the urinary bladder [43]. In 1976, Morales evaluated BCG in a small number of recurrent NMIBC patients and observed greater than 10-fold reduction in recurrence rates with weekly intravesical and intradermal BCG for 6 weeks [44]. In the 1980s,

randomized controlled trials examining the effectiveness of intravesical BCG (given after transurethral resection, TUR) for NMIBC versus surgical resection alone demonstrated a significantly reduced tumour recurrence rate with BCG therapy [45,46]. In one of these trials, BCG therapy was also found to reduce tumour progression [46].

Subsequent meta-analyses demonstrated that BCG therapy reduced the risk of bladder cancer recurrence, compared with TUR alone [47,48]. BCG therapy was also significantly more effective in preventing cancer recurrence when compared with chemotherapy [49,50]. In other meta-analyses, BCG therapy was found to prevent or slow down the progression of bladder cancer to a level greater than chemotherapy [51,52]. However, no significant differences between BCG and chemotherapy (mitomycin C) for cancer progression or survival were reported by Malmström et al. [53]. Variations in maintenance schedules of BCG, patient characteristics, follow-up period and statistical analyses were suggested to be responsible for these conflicting results [54]. Pertaining to maintenance schedules, it has been shown that maintenance BCG given over a 3-year period results in increased recurrence-free survival [55,56]. Based on these, a risk-stratified schedule (1-year and 3-year maintenance therapy for intermediate-risk and high-risk disease respectively) has been recommended for BCG therapy [57,58].

BCG therapy for bladder cancer also has some limitations. Response to BCG therapy is unpredictable and reliable biomarkers to accurately predict treatment outcome are needed. Studies have shown that BCG therapy fails in approximately 25% to 45% of patients and ~40% of patients initially responding to BCG therapy would relapse eventually [55,59-61]. BCG therapy also has side-effects most common of which are haematuria and cystitis, occurring in approximately 20% and 35% of cases, respectively [62]. Systemic adverse events include fatigue, general malaise, pyrexia and a transient flu-like illness. Severe systemic effects are rare and caused by disseminated infection [63,64]. At least 7 deaths due to BCG sepsis, nearly all attributed to inappropriate BCG administration, have been reported [65].

Melanoma

The use of BCG as an immunotherapy for melanoma was first attempted in the mid-20th century [13]. In 1970, Morton et al. [66] demonstrated a specific immune response in melanoma patients which was augmented with BCG therapy. Moreover, BCG therapy resulted in tumor regression in 6 out of 8 patients [66]. In 1972, intralesional BCG was shown to induce complete regression in 15% to 20% of melanoma patients [67,68]. In a larger study involving 36 patients, it was observed that 90% of the melanoma lesions underwent regression with direct BCG injection, compared with 17% of the non-injected lesions [69]. In 1993, pooled data from 15 studies showed that intralesional BCG led to complete responses in 19% and prolonged the survival in 13% of stage III melanoma patients [70]. In view of these findings, intralesional BCG therapy is listed in the National Comprehensive Cancer Network guidelines of the United States as an option for inoperable stage III melanoma [71].

Systemic BCG therapy has also been evaluated against melanoma. Many trials, wherein systemic BCG was given with cytotoxic drugs, cancer vaccines, or cytokine therapies, reported little advantage with co-administration of BCG [72,73]. However, a large study evaluating BCG with placebo versus Canvaxin (an allogeneic whole-cell vaccine developed from 3 melanoma cell lines) in 1,160 stage III and 496 stage IV melanoma patients indicated the beneficial effect of systemic BCG [74]. In an interim data analysis, the overall projected 5-year survival was 63% in stage III patients and 42% in stage IV patients, which was significantly higher than that typically seen in melanoma [74]. Higher-than-typically observed survival rates in both arms (BCG + placebo and BCG + Canvaxin) were also seen in the long-term follow-up of the stage IV patients who had undergone surgical resection. In another study on surgically resected stage I to III melanoma patients, no statistically significant differences in disease-free survival or overall survival were observed with BCG therapy [75].

More recently, intralesional BCG has been evaluated in a combinatorial approach with a variety of agents including imiquimod (a topical Toll-like receptor 7 agonist), ipilimumab (immune-check point inhibitor) and an experimental agent velimogene aliplasmid (a plasmid-lipid complex encoding human leukocyte antigen-B7 and β2-microglobulin) [76]. Higher rates of complete regression have been observed with BCG used in combination with imiquimod [77,78]. Recently, an update on a randomized phase II study has shown promising results in cutaneous melanoma patients treated with a cellular vaccine (Vaccimel) in combination with BCG and granulocyte-macrophage colony-stimulating factor [79].

Colorectal cancer

Colorectal cancer begins on the inner lining of the colon or rectum as a growth called polyps which may become cancerous over the period of many years. Early studies evaluating BCG against colorectal cancer were performed in the 1980s. In one of these studies, no significant differences in disease-free survival and overall survival were observed at 5 years of follow-up in control versus treatment group, which received vaccinations with BCG along with neuraminidase-treated autologous tumour cells [80]. Similar findings with oral BCG given alone or along with chemotherapy post-surgery were reported by Abdi et al. [81] in 1989. In 2000, a study by Harris et al. [82] demonstrated no significant clinical benefit with an autologous tumor cell-BCG vaccine in surgically resected stage II or III colon cancer patients. However, beneficial outcomes in terms of disease-free and overall survival benefits were observed in this study.

A subsequent multi-institutional, prospectively randomized,

controlled study using same vaccine reported significant clinical benefits in stage II colon cancer patients [83]. These findings were confirmed in a multicenter, randomized controlled phase III clinical trial, which reported significantly beneficial effects for all endpoints including recurrence-free interval, overall survival, and recurrence-free survival in stage II colon cancer patients [84]. This personalized immunotherapy approach consisting of irradiated autologous tumor cells with adjuvant BCG (OncoVAX; Vaccinogen Inc.) has been evaluated in a few subsequent studies [85]. A pivotal, randomized, multicenter phase IIIb clinical trial (NCT02448173) was conducted by recruiting participants to evaluate the beneficial effects of OncoVAX in stage II colon cancer patients post-surgery [86].

Lung cancer

Initial studies evaluating BCG or its cell wall skeleton for the treatment of lung cancer were undertaken in the 1970s. In 1976, McKneally et al. [87] observed that a single postoperative intrapleural dose of BCG in 38 patients was well tolerated in limited doses, and preliminary findings indicated significant benefit in patients with stage I cancer. In the same year, Yasumota et al. [88] demonstrated that the BCG cell wall skeleton mitigated lymphocyte suppression in lung cancer patients and prolonged the survival of patients with stage III or IV lung cancer or carcinomatous pleuritis. The beneficial effects of BCG or its cell wall skeleton in lung cancer patients were demonstrated by subsequent studies [89-91].

On the other hand, a few studies demonstrated that BCG lacks in efficacy and possibly enhances tumour growth in lung cancer patients [92-94]. This was followed by a sharp decline in interest in BCG for the treatment of lung cancer. A study has been undertaken to evaluate BCG in combination with anti-idiotypic antibody BEC2 for the treatment of patients with limited-stage small-cell lung cancer [95]. However, vaccination with Bec2/BCG did not impact the outcome in these patients [95].

Prostate cancer

Initial studies evaluating BCG against prostate cancer were undertaken in the late 1970s and demonstrated favourable responses [96]. In 1978, Guinan et al. [97] demonstrated that prostate cancer patients receiving BCG immunotherapy (in combination with conventional therapy) exhibited significantly elevated immune responses and cutaneous hypersensitivity reactions, compared with those receiving conventional therapy. In a 1979 study involving 46 BCG recipients and 46 matched controls, BCG therapy was found to prolong survival compared with controls (37 vs. 21 months) [98]. Significantly elevated complement levels and cutaneous hypersensitivity with BCG therapy suggested an immune-mediated effect [98]. Similar results were observed in a 1982 study wherein advanced prostate cancer patients receiving adjuvant BCG immunotherapy (plus conventional therapy) exhibited prolonged survival compared with the control (conventional estrogen therapy) group [99]. However, quality-of-life indicators were found to be significantly poorer in the BCG recipients. The next decades witnessed a declining interest in the use of BCG for prostate cancer.

MECHANISMS OF CANCER-PREVENTIVE EFFICACY OF BCG

To understand the mechanisms underlying BCG-mediated cancer prevention, it will be helpful to recall the role of immune system in protection from cancer and its pathogenesis. It is largely accepted that chronic inflammation acts as a carcinogen and predisposes the affected individual to the development of cancer [100]. In keeping with this, non-steroidal anti-inflammatory drugs have been shown to protect against cancer of esophagus, stomach, breast, lung, prostate, urinary bladder, and ovary. Interestingly, BCG has also been shown to mitigate inflammatory responses in different conditions including autoimmune diseases and coronavirus disease 2019 [101,102]. In mice fed with dextran sodium sulphate, freeze-dried BCG has been shown to control severe colitis by expanding T regulatory cell populations [103]. Importantly, a recent study has demonstrated that BCG protects from colorectal cancer by promoting anti-inflammatory response and altering gut microbiota [104].

As a tumor cell develops in the body, a complex interplay with the immune system ensues. The relationship between cancer the immune system has been defined by 3Es, which stand for elimination, equilibrium, and escape [4]. Most cells with tumorigenic potential are recognized and eliminated by the immune system, as they arise in the body. Sometimes, it may be difficult for the immune system to eliminate such cells for their newer clones keep arising, while older ones are being eliminated. This battle between the immune system and tumor cells results in a state of equilibrium, which may last for a long and resolve with the complete elimination of tumor cells. Occasionally, the state of equilibrium may proceed to immune escape, wherein tumor cells develop strategies to prevent their elimination by the immune system, often by suppressing the latter [4].

It can be argued that BCG effectuates primary cancer prevention by bolstering the immune system to lyse tumor cells during the elimination or equilibrium phase. Natural killer (NK) cells and $CD8^+$ T lymphocytes are the key players in antitumor immunity [4,105]. NK cells can recognize tumor cells based on the danger signals, whereas $CD8^+$ T lymphocytes recognize and eliminate these cells on the basis of their antigens, presented on MHC molecules [4,105]. Importantly, several studies have demonstrated that BCG can activate NK cells and enhance their cytolytic activity [106,107]. BCG vaccination has also been shown to result in enhanced production of proinflammatory cytokines by NK cells [107]. Supporting the role of NK cells in BCG-mediated protection

against cancer, the antitumor efficacy of BCG is drastically reduced in NK cell-deficient or NK cell-depleted mice [106]. Macrophages can also recognize tumor cells based on specific cell surface markers and possess potent cytolytic mechanisms. Interestingly, BCG has been shown to promote macrophage cytotoxicity against tumor cells [108]. Besides, BCG promotes T_H1 type of immune responses, which can restrict tumor cell growth or promote tumor cell elimination by activating multiple pathways in immune and non-immune cell types including tumor cells [109,110].

Studies with bladder cancer patients have provided valuable insights into the underlying mechanisms of tertiary cancer prevention by BCG. It has been demonstrated that after instillation in the bladder, BCG interacts with urothelial cells through cell-surface molecules such as fibronectin and integrin $\alpha5\beta1$, and is internalized by tumor cells. Subsequently, BCG can directly kill tumor cells or induce cytokine/chemokine secretion and MHC class II expression in them. Inflammatory cytokines and chemokines produced by tumor cells (or a few locally present myeloid cells) stimulate the recruitment of immune cells, including NK cells and $CD8^+$ T lymphocytes into the vicinity of tumor cells. Orchestrated attack by activated immune cells eliminates the tumor cells and as an outcome, prolongs the relapse-free survival. The mechanisms underlying primary and tertiary cancer prevention by BCG are illustrated in the Figure 1. It is likely that similar mechanisms are involved in the efficacy of BCG against other cancer types.

An important aspect of BCG vaccine is that its protective efficacy in case of TB is highly variable, ranging from nil to 80%. Interestingly, studies have shown that it is effective against leprosy even in the areas of poor anti-TB efficacy. Although why BCG exhibit such a variable efficacy remains poorly understood, it has been hypothesized that EMb modulates the efficacy of BCG by masking or blocking its immune-activating potential. We have previously postulated that BCG exhibits poor efficacy in the EMb-abundant regions, for inhabitants in these regions develop an aggravated antimycobacterial immunity which drives TB pathogenesis. It is plausible that variable cancer-preventive efficacy of BCG as observed by different researchers might be, at least partly, due to the similar effects of EMb.

CONCLUSION AND FUTURE PERSPECTIVES

BCG is one of the most widely used vaccines. Although it was developed as a prophylactic vaccine against TB, it has been evaluated against other disease conditions. In the case of cancer, it has been examined for primary prevention of malignancies and as an immunotherapeutic agent. Many previous studies have demonstrated a mixed response to BCG in terms of primary cancer prevention. In a recent 60-year follow-up study, BCG has been found to result in significant

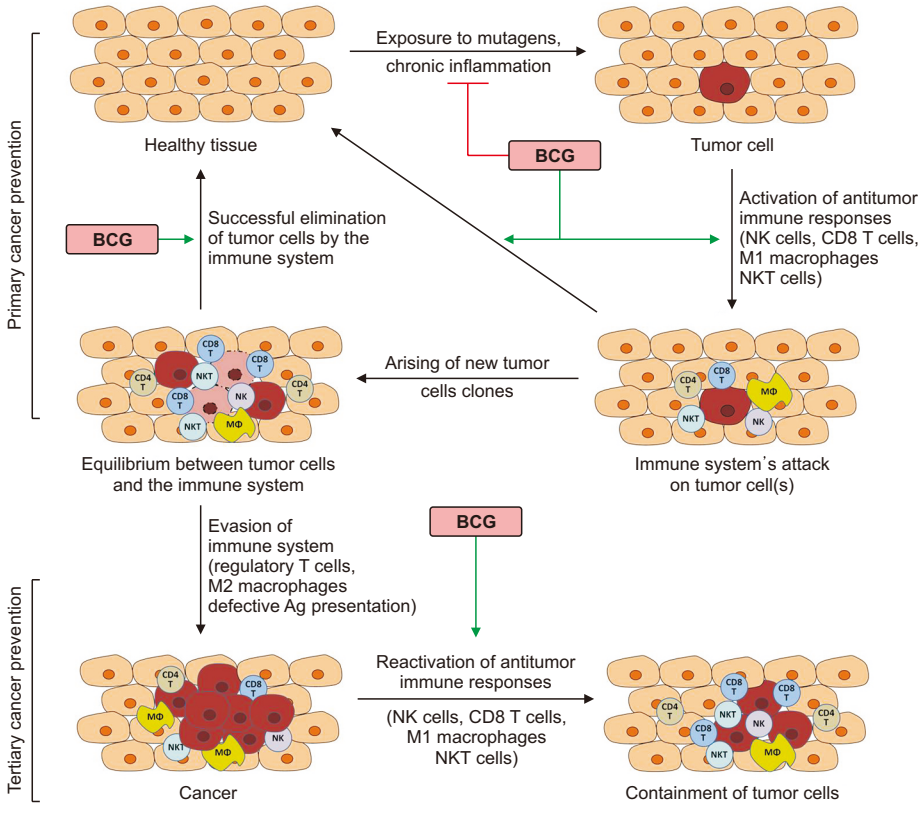

Figure 1. Modulation of cancer-immune system interaction and cancer prevention by Bacillus Calmette-Guérin (BCG). Available data suggests that BCG effectuates primary cancer prevention by mitigating chronic inflammation and by bolstering the immune system to eliminate tumor cells. Also, BCG can tilt the balance towards elimination of tumor cells by the immune system during the equilibrium phase. BCG can reactivate the immune system in cancers with an immunosuppressive microenvironment. Containment of tumor cells by the reactivated immune system results in tertiary cancer prevention as observed in the case of non-muscle invasive bladder cancer. NK, natural killer.

protection against lung cancer development, even though overall cancer incidence was comparable with the control group. BCG has also been evaluated for tertiary cancer prevention and has been found to be significantly effective against NMIBC. However, it has shown a mixed response against other cancer types. Why BCG has exhibited variable cancer preventive efficacy in different studies remains poorly understood. It is noteworthy that the efficacy of BCG is highly variable even in the case of TB, and a role of EMb has been implicated in it. It is plausible that similar mechanisms might be responsible for the variable efficacy of BCG in cancer prevention.

It is also worth mentioning the last 2 to 3 decades have witnessed a sea-change in living conditions and life-style across the globe. Moreover, these changes have been suggested as a driving force for many non-communicable diseases including cancer. In such a scenario, it may be worth re-evaluating BCG for its efficacy in preventing different cancers. Also, many cancer antigens have been characterized and can be used for specifically targeting cancer cells using a recombinant antigen-expressing BCG. It is likely that recombinant BCG will have a markedly different modulatory effect on host immune response (compared with what was observed in the 1970s or 80s) and will potentially activate tumor-specific immune responses, resulting in its significantly enhanced efficacy in primary and tertiary cancer prevention.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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